

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/12	A1	(11) International Publication Number: WO 97/47286 (43) International Publication Date: 18 December 1997 (18.12.97)
(21) International Application Number: PCT/US97/09471 (22) International Filing Date: 2 June 1997 (02.06.97) (30) Priority Data: 9612297.3 11 June 1996 (11.06.96) GB (71) Applicant (for all designated States except US): MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; 3M Center, P.O. Box 33427, Saint Paul, MN 55133-3427 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): OLIVER, Martin, J. [GB/GB]; 37 St. Leonards Road, Clarendon Park, Leicester LE2 1WS (GB). PALING, Simon, G. [GB/GB]; 23 Garendon Avenue, Hathern, Leicester LE12 5HT (GB). JINKS, Philip, A. [GB/GB]; 91 Rockhill Drive, Mountsorrel, Leicester LE12 7DS (GB). JAISWAL, Sukhbinder, K. [GB/GB]; 2 Lytton Road, Clarendon Park, Leicester LE2 1WH (GB). (74) Agents: RINGSRED, Ted, K. et al.; Office of Intellectual Property Counsel, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MEDICINAL AEROSOL FORMULATIONS OF FORMOTEROL		
(57) Abstract A pharmaceutical suspension formulation suitable for aerosol administration having from 0.0025 to 0.1 % w/w of micronized Formoterol, or an acid addition salt thereof, from 0.1 to 5.0 % w/w ethanol, HFA 134a, HFA 227 or a mixture of HFA 227 and HFA 134a, and optionally a surfactant other than a monoacetylated or diacetylated monoglyceride, the formulation being further characterized in that it exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, is substantially and readily redispersible, and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug.		

Best Available Copy

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

MEDICINAL AEROSOL FORMULATIONS OF FORMOTEROL

Field of the Invention

This invention relates to medicinal aerosol formulations and in particular to
5 aerosol formulations containing Formoterol Fumarate which are suitable for
administration to the respiratory system of a patient.

Background

Most pharmaceutical suspension aerosol formulations currently use a
10 mixture of liquid chlorofluorocarbons as the propellant. Fluorotrichloromethane,
dichlorodifluoromethane and dichlorotetrafluoroethane are the most commonly
used propellants in aerosol formulations for administration by inhalation.

Chlorofluorocarbons (CFCs), however, have been implicated in the
destruction of the ozone layer and their production is being phased out.
15 Hydrofluorocarbon 134a (HFA 134a, 1,1,1,2-tetrafluoroethane) and
hydrofluorocarbon 227 (HFA 227, 1,1,1,2,3,3,3-heptafluoropropane) are viewed as
being more ozone friendly than many chlorofluorocarbon propellants; furthermore,
they have low toxicity and vapor pressures suitable for use in aerosols.

W091/11495 and W091/11496 disclose pharmaceutical suspension aerosol
20 formulations comprising a medicinal agent, a surfactant, and a propellant mixture
containing 1,1,1,2,3,3,3-heptafluoropropane and one or more additional
components, e.g. pentane, butane, propellant 134a, propellant 11, propellant 125,
or propellant 152a.

EP 0384371 discloses solution aerosols in which 1,1,1,2,3,3,3-
25 heptafluoropropane or its mixture with propane, butane, isobutane, dimethyl ether,
or 1,1,1,2,3,3,3-heptafluoropropane serves as the propellant. The application does not, however,
disclose suspension aerosols or pharmaceutical aerosol formulations.

EP 0372777 discloses, inter alia, aerosol formulations comprising a
medicament, 1,1,1,2-tetrafluoroethane, a surface active agent, and at least one
30 compound having higher polarity than 1,1,1,2-tetrafluoroethane.

U.S. 2,868,691 discloses aerosol formulations comprising a medicament, a halogenated lower alkane propellant, and a co-solvent which assists in dissolving the medicament in the propellant. The chemical formula for the propellant given in column 2, lines 6 to 16, generically embraces HFA 134a and HFA 227. Examples of co-solvents disclosed include ethanol and diethyl ether.

U.S. 3,014,844 discloses aerosol formulations comprising a micronised medicament, a halogenated lower alkane propellant and a surface-active agent to assist in the suspension of the medicament in the propellant. The chemical formula for the propellant given in column 4, lines 17 to 28, generically embraces HFA 134a and HFA 227.

W091/04011 discloses aerosol compositions having HFA 134a as the propellant and comprising a medicament coated with a non-perfluorinated surface active dispersing agent.

W093/11747 discloses a pharmaceutical suspension formulation suitable for aerosol administration, consisting essentially of a therapeutically effective amount of a drug and a propellant selected from the group consisting of HFA 134a, HFA 227, and a mixture thereof, the formulation being further characterized in that it exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, is substantially and readily redispersible, and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug. The application specifically discloses formulations of Formoterol Fumarate in HFA 134a, HFA 227 and 1 : 1 mixtures of HFA 134a and HFA 227. The formulations do not contain surfactants or ethanol. It is stated that mixtures of HFA 134a and HFA 227 may be adjusted for density matching with the drug.

W093/11745 discloses pharmaceutical aerosol formulations, substantially free of surfactant containing fluorocarbon or hydrogen-containing chlorofluorocarbon propellants and up to 5% of a polar co-solvent. Preferred propellants are HFA 134a and HFA 227 which are preferably used alone. The preferred polar co-solvent is ethanol and it is stated that in general only small quantities e.g. 0.05 to 3.0% w/w of polar co-solvent are required to improve the

dispersion and the use of quantities in excess of 5% w/w may disadvantageously tend to dissolve the medicament.

EP-A-0504112 discloses a pharmaceutical composition for aerosol use containing:

- 5 (a) a liquefied propellant gas or propellant gas mixture with a vapor pressure exceeding 1 bar but less than 6 bar (20°C) from the unsubstituted or partially to completely fluorinated hydrocarbon group;
- (b) a non-ionic tensile of the monoacetylated or diacetylated
10 monoglyceride group;
- (c) a pharmaceutical active substance or combination of active substances, and, if necessary,
- (d) other common pharmaceutical accessory substances suitable for aerosol formulations.

15 It is stated the basic purpose of that invention was to find a special accessory suspending substance for active substances in aerosol formulations, which dissolves better in liquefied "alternative" propellant gases than the accessory suspending substances hitherto recognized and used. Surprisingly, it was discovered, in solving this problem, that non-ionic tensides of the monoacetylated
20 or diacetylated monoglyceride group are very soluble in the "alternative" propellant gases mentioned, particularly in heptafluoropropane (HFA 227), are beneficial to the production of homogenous suspensions, and also have outstanding metering valve lubrication properties. Some of the examples of EP-A-0504112 disclose formulations comprising Formoterol Fumarate.

25 Formoterol Fumarate is a long acting B₂ agonist which has been developed for delivery to the respiratory system by a metered dose inhaler (MDI). The drug is highly potent and its dosage is considerably less than many other drugs which have been administered by MDIs. Thus, the concentration of Formoterol Fumarate in aerosol formulations is very low and this factor, together with other properties of
30 the drug have led to problems in manufacturing and formulating a composition

which is stable and provides good dosage reproducibility when administered by MDIS.

Aerosol formulations consisting of propellant, e.g. HFA 134a, HFA 227 and mixtures thereof, and Formoterol Fumarate without additional excipient sometimes encounter problems such as caking on manufacturing equipment, high deposition in the vial or valve of inhalers and valve sticking.

Aerosol compositions consisting of Formoterol Fumarate, HFA 134a and ethanol have proved to be extremely sensitive to ethanol concentration. An ethanol concentration of 3.5% w/w may cause unacceptable crystal growth.

Summary of the Invention

It is an object of the present invention to provide stable aerosol compositions containing Formoterol Fumarate.

According to one aspect of the present invention there is provided a pharmaceutical suspension formulation suitable for aerosol administration, consisting essentially of:

- (a) from 0.0025 to 0.1% w/w of micronized Formoterol, or an acid addition salt thereof and
- (b) from 0.1 to 5.0% w/w ethanol,
- (c) HFA 134a, HFA 227 or a mixture of HFA 227 and HFA 134a and optionally
- (d) a surfactant other than a monoacetylated or diacetylated monoglyceride,

the formulation being further characterized in that it exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, is substantially and readily redispersible, and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug.

According to a second aspect of the invention, there is provided a pharmaceutical suspension formulation suitable for aerosol administration, consisting essentially of:

- (a) from 0.0025 to 0.1% w/w of micronised Formoterol, or an acid addition salt thereof,
- (b) from 0.1 to 5.0% w/w ethanol,
- (c) a propellant consisting of HFA 134a, HFA 227 or a mixture of HFA 227 and HFA 134a,
- (d) a micronised bulking agent in a weight ratio in the range from 1 : 3 to 1 : 100 of Formoterol : bulking agent, and optionally
- (e) a surfactant,

the formulation being further characterized in that it exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, is substantially and readily redispersible, and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug.

Detailed Description

It has been found that improved aerosol formulations comprising Formoterol Fumarate may be obtained by utilizing low concentrations of ethanol. The combination of HFA 134a and HFA 227 in a weight ratio of HFA 134a : 227 from 50 : 50 to 30 : 70 provides a propellant system in which the drug has good stability. The preferred ratio is about 37.5 : 62.5.

Alternatively, stable formulations may be obtained by the incorporation of a micronised bulking agent which will sediment in the propellant e.g. lactose, DL-Alanine, ascorbic acid, glucose and D+ trehalose dehydrate. The micronised bulking agent may prevent the drug from creaming by co-flocculating with the drug, the resultant flocs are denser than the propellant and will sediment leaving no creamed layer upon prolonged standing. The weight ratio of drug to bulking agent is in the range 1 : 3 to 1 : 100, generally from 1 : 3 to 1 : 20. If the concentration of bulking agent is too low, not all of the drug will sediment and a small amount will cream. If the concentration is too high, the formulation may flocculate and either sediment or cream too quickly for acceptable use as an aerosol formulation.

The presence of ethanol assists in the stability, the general performance and in the manufacturing of the formulation. Preferably ethanol is present at a concentration in the range 1.5 to 3.5%, more preferably about 2.5% w/w in formulations which do not employ bulking agent. In formulations containing bulking agent ethanol is generally present at about 1% w/w as this has been sufficient to provide the above benefits.

The composition of the invention may comprise a surfactant. Low levels of surfactant, often below the levels normally used for the purposes of stabilizing suspensions and valve lubrication in aerosol formulations, have been shown surprisingly to provide a flocculant effect to produce stable floccular dispersions. Levels of oleic acid of 0.002 to 0.01% w/w have provided useful properties, a preferred concentration is about 0.005% w/w. Other surfactants and/or larger levels of surfactant may be used.

The concentration of Formoterol Fumarate depends upon the dose required and the metering volume of the valve. Concentrations of 0.01% w/w and 0.02% w/w have proved to be suitable, using a 50 microlitre valve.

It is conventional practice when preparing aerosol formulations to mix the drug with the highest boiling point material and thereafter mix with the propellant. However, when making the formulations of the present invention it is important to ensure the Formoterol Fumarate does not come into contact with high concentrations e.g. above 10% w/w, of ethanol since the drug would dissolve leading to instability and crystal growth problems in the final formulation. Preferably the maximum concentration of ethanol during formulation is less than 5%. A suitable method for manufacturing formulations on a pilot scale is as follows.

The ingredients are divided into those for making the concentrate and those for including in the bulk.

The concentrate contains the drug and optional bulking agent, sufficient propellant to disperse them and ethanol, preferably not in excess of 5 percent of the weight of the concentrate, more preferably about 2.5% The bulk contains most of the propellant, the balance of the ethanol and optional surfactant.

The bulk ingredients are fed into a batching vessel, which is either chilled to approximately -55°C for the purposes of cold filling, or is pressure resistant for pressure filling.

In a glove box purged with dried air, a small quantity of propellant is added to a prechilled stainless steel concentrate vessel. Prechilled ethanol is added. A homogenizer is inserted into the concentrate vessel. Prew weighed drug and optional bulking agent are added slowly to disperse. This forms the concentrate.

After dispersing, the concentrate is added to the bulk propellant in the batching vessel and mixed continuously until all of the formulation has been dispensed.

The bulk formulation is either dispensed chilled into open aluminum cans, which are immediately sealed with a metering valve on each can, or pressure filled into cans which have previously been sealed with metering valves.

The invention will be illustrated by the following Examples.

In the Examples, unless otherwise stated, the following preparation technique was employed.

The formulations were prepared in the laboratory by dispensing the active and if required the bulking agent into a preweighed vial. This was then sealed with a non-metering valve and the premixed ethanol/propellant and optional surfactant injected into the vial. The vial was then subjected to ultrasonic energy to disperse the solid particles.

Examples 1 to 5

The following formulations were prepared (FF denotes Formoterol Fumarate):

	Example 1	Example 2	Example 3	Example 4	Example 5
	%w/w	%w/w	%w/w	%w/w	%w/w
FF	0.010	0.010	0.010	0.010	0.010
Ethanol	2.500	2.500	2.500	2.500	2.500
HFA 227	48.745	65.806	63.368	60.931	56.057
HFA 134a	48.745	31.684	34.121	36.559	41.433
	100.00	100.00	100.00	100.00	100.00

Measured Density of Formulations (g/ml)

Example	Temperature (Deg. C)			Propellant ratio (w/w)	
	20	25	30	HFA 227	HFA 134a
1	1.285	1.266	1.247	50.0	50.0
5	1.298	1.279	1.259	57.5	42.5
4	1.307	1.288	1.269	62.5	37.5
3	1.312	1.293	1.272	65.0	35
2	1.317	1.298	1.277	67.5	32.5

The above formulations were designed such that the density of the liquid component was fairly close to that of Formoterol Fumarate.

5 These formulations had the following creaming and sedimenting characteristics at 20°C.

Formulation 1 just sedimented. Formulation 2 creamed. Formulation 4 gradually creamed at 20°C but gradually settled at 30°C when observed over a 12 hour period.

10 Each formulation was tested for uniformity of drug dosing, after storage periods of up to 24 hours at ambient temperature in order to simulate patient use. Formulation 4 gave the most consistent performance in these tests.

Formulations containing oleic acid

15 The following formulations were prepared:

	Example 4	Example 6	Example 7	Example 8	Example 9
	%w/w	%w/w	%w/w	%w/w	%w/w
FF	0.010	0.010	0.010	0.010	0.010
Oleic Acid	0	0.0001	0.0003	0.0005	0.001
Ethanol	2.500	2.500	2.2500	2.500	2.500
HA 227	60.931	60.931	60.931	60.931	60.931
HFA 134a	36.559	36.559	36.559	36.559	36.558
	100.000	100.000	100.000	100.000	100.000

	Example 10	Example 11	Example 12	Example 13	Example 14	Example 15
	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w
FF	0.010	0.010	0.010	0.010	0.010	0.010
Oleic Acid	0.002	0.003	0.004	0.005	0.007	0.009
Ethanol	2.500	2.500	2.500	2.500	2.500	2.500
HFA 227	60.930	60.929	60.929	60.928	60.927	60.926
HFA 134a	36.558	36.558	36.557	36.557	36.556	36.555
	100.000	100.000	100.000	100.000	100.000	100.000

The formulations had the following characteristics:

Low levels of oleic acid have been shown surprisingly to impart a flocculant effect to produce stable floccular dispersions, which may allow less migration of drug to and from the metering chamber of the valve than surfactant-free formulations. This is because the floc size of the formulations is larger. visual differences were apparent for surfactant levels when comparing 0% oleic acid with 0.005 to 0.009% oleic acid. Formulations containing 0.0001 to 0.001% oleic acid showed no difference from the 0% oleic acid formulation, when examined either visually or by using an optical measuring technique such as that described in the Proceedings of Drug Delivery to the Lung VI p.10-13 (Dec. 1995) printed by The Aerosol Society. Examples 9 to 13 having 0.001% to 0.005% in steps of 0.001% oleic acid showed increasing effect, which was measurable at the 0.002% level in Example 10.

Examples 16 to 22

Use of Bulking Agent

In order to study the suspension characteristics of lactose bulked formulations a range of units was prepared. The ratio of Formoterol Fumarate (FF) to lactose (L) was varied between 1 : 1 and 1 : 7 and suspended in a mixture of Ethanol : HFA 227, 1 : 99 using the following formulations:

Example	16	17	18	19	20	21	22
FF : L	1 : 1	1 : 2	1 : 3	1 : 4	1 : 5	1 : 6	1 : 7
	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w
FF	0.009	0.009	0.009	0.009	0.009	0.009	0.009
Lactose	0.009	0.019	0.028	0.038	0.047	0.056	0.066

All formulations were made up to 100% with Ethanol : HFA 227 at 1 : 99 by weight.

The following method was used to prepare the formulations:

- 5 i) The propellant mix was made up in a 500ml can by first weighing out 1g of ethanol and crimping on a 1 inch continuous valve. 99g of HFA 227 was then injected into the can through the valve.
- ii) The Formoterol Fumarate and the lactose were weighed directly into transparent vials.
- iii) A non-metering valve was crimped onto each vial.
- 10 iv) The vials were filled with the prescribed amount of propellant mix from the 500ml can using a transfer button, to transfer some propellant mix via the valves of the can and the vial.
- v) The vials were placed in an ultrasonic bath for four minutes to homogenize the formulation.

15 Result

The resulting suspensions were examined visually.

They were found to form fairly coarse flocs, which tended to sediment. The sedimentation rate increased with lactose concentration. For weight ratios of greater lactose content than 1 : 7, more rapid sedimentation would occur which
20 could lead to a general loss of dosing reproducibility.

Formulations 19 and 22 were tested for uniformity of drug dosing, after storage periods up to 24 hours, in order to simulate patient use. Formulation 22 gave the most consistent performance in these tests.

25 Examples 23 and 24

Effect of different ethanol concentration with bulking agent

The formulation of Example 22 (1% ethanol) was compared with formulations containing 2 and 3% ethanol. The following formulations were prepared:

Example	22	23	24
Percentage of ethanol	1%	2%	3%
%w/w			
FF	0.009	0.009	0.0009
Lactose	0.066	0.066	0.066
Ethanol	1.000	2.000	3.000
HFA 227	98.925	97.925	96.924
	100.000	100.000	100.000

Results

No visual difference was observed in the size of the flocs or the floc settling rate obtained with the three concentrations of ethanol used. Thus the beneficial effects of adding ethanol were realized by including the minimum amount (i.e. 1% ethanol).

Example 25

Use of Different Bulking Agents with Formoterol Fumarate Suspension

Formulation	%w/w
FF	0.009
Bulking agent	0.066
Ethanol	1.000
HFA 227	98.925
HFA 134.a	
	100.000

The bulking agent was selected from the following list, which also gives densities determined by Pycnometry.

Sample	Density, g/ml
DL-Alanine	1.3963
Ascorbic acid	1.6955
Glucose (dextrose)	1.5264
Lactose, monohydrate	1.5379
D(+) Trehalose dihydrate	1.5036

The Alanine bulked formulation formed flocs more slowly than either of the two Lactose bulked formulations which could improve dosing characteristics. The flocs were suspended in the vial, and appeared to be density matched at the laboratory temperature of 22°C.

All of the other bulking agents examined formed rapidly flocculating suspensions, which then sedimented.

Examples 26 to 28

5 Alanine bulking agent with propellant mixtures.

The following formulations were prepared:

Example	26	27	28
Propellant ratio (w/w)	62.5% HFA 227 37.5% HFA 134a	75% HFA 227 25% HFA 134a	100% HFA 227
%w/w			
FF	0.10	0.10	0.009
bulking agent	0.069	0.068	0.066
Ethanol	1.000	1.000	1.000
HFA 227	61.826	74.192	98.925
HFA 134a	37.095	24.731	
	100.000	100.000	100.000

Visual Assessment

10 The resultant suspensions were examined visually. As before, the Alanine suspensions formed smaller flocs, which formed more slowly than those of the Lactose bulked suspensions. At the laboratory temperature of 25°C, the suspensions in Example 28 appeared to rise towards the surface of the liquid, although a creamed layer was not observed.

15 Example 27 appeared to be density matched, with the flocs gradually settling to the bottom of the vial. Example 26 settled to the bottom of the vial more rapidly.

On standing overnight, Example 28 had creamed and formed a layer occupying approximately the top third of the liquid layer. In the two suspensions with lower HFA 227 ratios, the flocs had settled to the bottom of the vial.

20 Thus, the use of Alanine allows the preparation of formulations in which the density of the suspended solids is a close match to that of the liquid component. Furthermore, the volume of sedimented or creamed solids is found to be advantageously larger than for formulations without such a density match.

The slower flocculation rate of suspended Alanine permits higher levels of it to be used as a bulking agent without causing undesirably rapid flocculation of the drug formulation, for example in a ratio of 1 : 100 drug : Alanine.

5

Examples 29 to 33

The following formulations were prepared:

Example	29	30	31	32	33
	%w/w	%w/w	%w/w	%w/w	%w/w
FF	0.011	0.011	0.011	0.009	0.009
Oleic acid	0.000	0.000	0.010	0.000	0.000
Ethanol	1.000	2.000	2.499	1.000	2.000
HFA 134a	98.989	97.989	97.480		
HFA 227				98.991	97.991
	100.000	100.000	100.000	100.000	100.000

The formulations of Examples 29 to 31 produced well dispersed, slowly flocculating suspensions which gradually sedimented. The presence of surfactant increased the floc size.

10

The formulations of Examples 32 and 33 produced well dispersed, slowly flocculating suspensions which gradually creamed.

CLAIMS

1. A pharmaceutical suspension formulation suitable for aerosol administration, consisting essentially of:

- 5 (a) from 0.0025 to 0.1% w/w of micronized Formoterol, or an acid addition salt thereof and
- (b) from 0.1 to 5.0% w/w ethanol,
- (c) HFA 134a, HFA 227 or a mixture of HFA 227 and HFA 134a and optionally
- 10 (d) a surfactant other than a monoacetylated or diacetylated monoglyceride,

the formulation being further characterized in that it exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, is substantially and readily redispersible, and upon redispersion does not

15 flocculate so quickly as to prevent reproducible dosing of the drug.

2. An aerosol formulation as claimed in Claim 1 which comprises HFA 134a and HFA 227 in a weight ratio of HFA 134a : HFA 227 in the range 50 : 50 to 30 : 70.

20

3. An aerosol formulation as claimed in Claim 2 in which the weight ratio of HFA 134a : HFA 227 is about 37.5 : 62.5.

4. An aerosol formulation as claimed in any preceding claim which

25 comprises about 1 to 5% w/w ethanol.

5. An aerosol formulation as claimed in any preceding claim which comprises about 0.01% w/w Formoterol Fumarate.

30 6. An aerosol formulation as claimed in any preceding claim which comprises oleic acid.

7. An aerosol formulation as claimed in Claim 6 in which the oleic acid is present in an amount of from 0.002 to 0.010% w/w.

5 8. An aerosol formulation as claimed in Claim 6 in which the oleic acid is present in an amount of about 0.005% w/w.

9. An aerosol composition as claimed in Claim 1 consisting of:

	Formoterol Fumarate	0.010
10	Ethanol	2.500
	HFA 227	60.931
	HFA 134a	36.559

10. An aerosol composition as claimed in Claim 1 consisting of:

15	Formoterol Fumarate	0.010
	Oleic Acid	0.005
	Ethanol	2.500
	HFA 227	60.928
	HFA 134a	36.557

20 11. A pharmaceutical suspension formulation suitable for aerosol administration, consisting essentially of:

- (a) from 0.0025 to 0.1% w/w of micronized Formoterol, or an acid addition salt thereof,
- 25 (b) from 0.1 to 5.0% w/w ethanol,
- (c) a propellant consisting of HFA 134a, HFA 227 or a mixture of HFA 227 and HFA 134a,
- (d) a micronized bulking agent in a weight ratio in the range from 1:3 to 1:100 of Formoterol bulking agent, and optionally
- 30 (e) a surfactant,

the formulation being further characterized in that it exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, is substantially and readily redispersible, and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug.

5

12. A pharmaceutical suspension formulation as claimed in Claim 11 comprising about 1% ethanol.

10

13. A pharmaceutical suspension formulation as claimed in Claim 11 or Claim 12 in which said weight ratio of Formoterol Fumarate to bulking agent is in the range 1 : 4 to 1 : 20.

15

14. A pharmaceutical suspension formulation as claimed in Claim 13 in which said weight ratio of Formoterol Fumarate to bulking agent is about 1 : 7.

20

15. A pharmaceutical suspension formulation as claimed in any one of Claims 11 to 14 in which the bulking agent is selected from lactose, DL-Alanine, ascorbic acid, glucose and D+ trehalose dehydrate.

16. A pharmaceutical suspension formulation as claimed in Claim 15 in which the bulking agent is lactose or DL-Alanine.

25

17. A pharmaceutical suspensions formulation as claimed in any one of Claims 11 to 16 in which the propellant is HFA 227.

18. A pharmaceutical suspension formulation as claimed in Claim 11 consisting of:

30

Formoterol Fumarate	0.132
Lactose	0.924
Ethanol	14.058
HFA 227	1390.686

19. An aerosol formulation substantially as herein described with reference to the Examples.

5 20. An aerosol dispensing device comprising a container equipped with a metered dose dispensing valve and containing an aerosol formulation as claimed in any preceding claim.

10 21. A method of making an aerosol formulation as claimed in any one of Claims 1 to 19 which comprises admixing the components in a manner such that Formoterol Fumarate does not come into contact with a concentration of ethanol greater than 10.0% w/w.

15 22. A method of making an aerosol formulation as claimed in Claim 21 which comprises admixing the components in a manner such that Formoterol Fumarate does not come into contact with a concentration of ethanol greater than 5% w/w.

20 23. A method as claimed in Claim 21 or Claim 22 in which Formoterol Fumarate and optionally bulking agent is mixed with a portion of the propellant and thereafter admixed with ethanol and the remainder of the propellant. 24. A method of preparing an aerosol formulation substantially as herein described with reference to the Examples.

25

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/09471

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 11747 A (MINNESOTA MINING & MFG) 24 June 1993 cited in the application see the whole document	1-10, 19-24
Y	---	1-24
Y	EP 0 504 112 A (CIBA GEIGY AG ;JAGO PHARMA AG (CH)) 16 September 1992 cited in the application see claims 1-3; examples 1-12	1-11
Y	WO 91 11173 A (FISONS PLC) 8 August 1991 see the whole document ---	1-24
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

1 October 1997

Date of mailing of the international search report

27. 10. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/09471

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 11745 A (GLAXO GROUP LTD) 24 June 1993 cited in the application see page 5, line 21-24 see page 3, line 6; examples 18-27 ---	1-10, 19-24
P,X	WO 96 18384 A (GLAXO GROUP LTD ;SAPSFORD ANDREW (GB); SAVAGE ANDREW PATRICK (GB)) 20 June 1996 see page 2, line 26 see page 3, line 31 - page 4, line 4 see page 3, line 20-22; claims 1-6 ---	1-10, 19-24
P,X	WO 96 19968 A (GLAXO GROUP LTD ;GREEN ALEXANDER PETER (GB)) 4 July 1996 see page 2, line 32 see page 5, line 16-22 see page 5, line 6-9 -----	11-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US 97/09471

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311747 A	24-06-93	AT 150296 T	15-04-97
		AU 1234297 A	20-03-97
		AU 3272893 A	19-07-93
		CA 2126244 A	24-06-93
		DE 69218455 D	24-04-97
		EP 0617610 A	05-10-94
		EP 0717987 A	26-06-96
		ES 2099415 T	16-05-97
		JP 7502275 T	09-03-95
		NZ 246421 A	28-05-96
EP 0504112 A	16-09-92	AU 646723 B	03-03-94
		AU 1218892 A	17-09-92
		CA 2062854 A	15-09-92
		JP 4327527 A	17-11-92
		MX 9201082 A	01-09-92
WO 9111173 A	08-08-91	AT 125153 T	15-08-95
		CA 2074495 A	03-08-91
		DE 69111426 D	24-08-95
		DE 69111426 T	18-01-96
		EP 0513127 A	19-11-92
		ES 2075956 T	16-10-95
		IE 67185 B	06-03-96
		IL 97065 A	25-01-94
		JP 5503523 T	10-06-93
		MX 24390 A	01-04-93
WO 9311745 A	24-06-93	AT 128350 T	15-10-95
		AU 663906 B	26-10-95
		AU 3085292 A	19-07-93
		CA 2125665 A	24-06-93
		DE 69205177 D	02-11-95
		DE 69205177 T	21-03-96
		EP 0616525 A	28-09-94
		ES 2079210 T	01-01-96
		JP 7501811 T	23-02-95
		MX 9207200 A	01-07-93
		NZ 246046 A	21-12-95
		ZA 9209618 A	09-08-93

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/09471

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311745 A		AP 402 A	22-08-95
		AU 663904 B	26-10-95
		AU 3085092 A	19-07-93
		AU 663905 B	26-10-95
		AU 3085192 A	19-07-93
		BG 98803 A	28-02-95
		CA 2125666 A	24-06-93
		CA 2125667 A	24-06-93
		CN 1075078 A	11-08-93
		CN 1075079 A	11-08-93
		CZ 9401430 A	15-03-95
		WO 9311743 A	24-06-93
		WO 9311744 A	24-06-93
		EP 0616523 A	28-09-94
		EP 0616524 A	28-09-94
		EP 0756868 A	05-02-97
		HU 67534 A	28-04-95
		HU 9500331 A	28-09-95
		JP 7502033 T	02-03-95
		JP 7502034 T	02-03-95
		MX 9207205 A	01-11-93
		NO 942185 A	10-06-94
		NZ 246044 A	26-01-96
		OA 9926 A	15-09-94
		SK 67494 A	08-03-95
		US 5658549 A	19-08-97
		US 5653962 A	05-08-97
WO 9618384 A	20-06-96	AU 4260496 A	03-07-96
		EP 0789557 A	20-08-97
WO 9619968 A	04-07-96	AU 4346996 A	19-07-96

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.